HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ORENCIA safely and effectively. See full prescribing information for ORENCIA.

ORENCIA (abatacept)
for injection for intravenous use
injection, for subcutaneous use
Initial U.S. Approval: 2005

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Adult Rheumatoid Arthritis (2.1) 12/2013

----------INDICATIONS AND USAGE----------

ORENCIA is a selective T cell costimulation modulator indicated for:

Adult Rheumatoid Arthritis (RA) (1.1)

- moderately to severely active RA in adults. ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists (1.1).

Juvenile Idiopathic Arthritis (1.2)

- moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older. ORENCIA may be used as monotherapy or concomitantly with methotrexate (1.2).

Important Limitations of Use (1.3)

- should not be given concomitantly with TNF antagonists (1.3, 5.1).

----------DOSAGE AND ADMINISTRATION----------

Intravenous Administration for Adult RA (2.1)

Body Weight of Patient	Dose	Number of Vials
Less than 60 kg	500 mg	2
60 to 100 kg	750 mg	3
More than 100 kg	1000 mg	4

Subcutaneous Administration for Adult RA (2.1)

- Administer by subcutaneous injection once weekly with or without an intravenous loading dose. For patients initiating therapy with an intravenous loading dose, administer a single intravenous infusion (as per body weight categories above), followed by the first 125 mg subcutaneous injection given within a day of the intravenous infusion.
- Patients transitioning from ORENCIA intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Intravenous Administration for Juvenile Idiopathic Arthritis (2.2)

- Pediatric patients weighing less than 75 kg receive 10 mg/kg intravenously based on the patient's body weight. Pediatric patients weighing 75 kg or more should be administered ORENCIA following the adult intravenous dosing regimen, not to exceed a maximum dose of 1000 mg (2.2).

General Dosing Information for Intravenous Administration (2.1)

- Administer as a 30-minute intravenous infusion (2.1)
- Following initial dose, give at 2 and 4 weeks, then every 4 weeks (2.1)
- Prepare ORENCIA using only the silicone-free disposable syringe (2.3)
- Use only sterile water to reconstitute the powder (2.3)
- The reconstituted product must be administered using a filter (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- 250 mg lyophilized powder in a single-use vial for intravenous infusion (3)
- 125 mg/mL solution in a single-dose prefilled syringe (3)

----------CONTRAINDICATIONS----------

- None (4)

----------WARNINGS AND PRECAUTIONS----------

- Concomitant use with a TNF antagonist can increase the risk of infections and serious infections (5.1)
- Hypersensitivity, anaphylaxis, and anaphylactoid reactions (5.2)
- Patients with a history of recurrent infections or underlying conditions predisposing to infections may experience more infections (5.3, 8.5)
- Discontinue if a serious infection develops (5.3)
- Screen for latent TB infection prior to initiating therapy. Patients testing positive should be treated prior to initiating ORENCIA (5.3)
- Live vaccines should not be given concurrently or within 3 months of discontinuation (5.4)
- Patients with juvenile idiopathic arthritis should be brought up to date with all immunizations prior to ORENCIA therapy (5.4)
- Based on its mechanism of action, ORENCIA may blunt the effectiveness of some immunizations (5.4)
- COPD patients may develop more frequent respiratory adverse events (5.5)

----------ADVERSE REACTIONS----------

Most common adverse events (≥10%) are headache, upper respiratory tract infection, nasopharyngitis, and nausea (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Registry available. Based on animal data, may cause fetal harm (8.1).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2014

FULL PRESCRIBING INFORMATION: CONTENTS *

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Adult Rheumatoid Arthritis (RA)

ORENCIA® is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. ORENCIA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.

1.2 Juvenile Idiopathic Arthritis

ORENCIA is indicated for reducing signs and symptoms in pediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis. ORENCIA may be used as monotherapy or concomitantly with methotrexate (MTX).

1.3 Important Limitations of Use

ORENCIA should not be administered concomitantly with TNF antagonists. ORENCIA is not recommended for use concomitantly with other biologic rheumatoid arthritis (RA) therapy, such as anakinra.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Rheumatoid Arthritis

For adult patients with RA, ORENCIA may be administered as an intravenous infusion or a subcutaneous injection.

ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

For pediatric juvenile idiopathic arthritis, a dose calculated based on each patient's body weight is used [*see Dosage and Administration (2.2)*].

Intravenous Dosing Regimen

ORENCIA intravenous should be administered as a 30-minute intravenous infusion utilizing the weight range-based dosing specified in Table 1. Following the initial intravenous administration,

an intravenous infusion should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter.

Table 1: Dose of ORENCIA for Intravenous Infusion in Adult RA Patients

Body Weight of Patient	Dose	Number of Vials[a]
Less than 60 kg	500 mg	2
60 to 100 kg	750 mg	3
More than 100 kg	1000 mg	4

[a] Each vial provides 250 mg of abatacept for administration.

Subcutaneous Dosing Regimen

ORENCIA 125 mg should be administered by subcutaneous injection once weekly and may be initiated with or without an intravenous loading dose. For patients initiating therapy with an intravenous loading dose, ORENCIA should be initiated with a single intravenous infusion (as per body weight categories listed in Table 1), followed by the first 125 mg subcutaneous injection administered within a day of the intravenous infusion.

Patients transitioning from ORENCIA intravenous therapy to subcutaneous administration should administer the first subcutaneous dose instead of the next scheduled intravenous dose.

2.2 Juvenile Idiopathic Arthritis

Intravenous Dosing Regimen

The recommended dose of ORENCIA for patients 6 to 17 years of age with juvenile idiopathic arthritis who weigh less than 75 kg is 10 mg/kg intravenously calculated based on the patient's body weight at each administration. Pediatric patients weighing 75 kg or more should be administered ORENCIA following the adult intravenous dosing regimen, not to exceed a maximum dose of 1000 mg. ORENCIA should be administered as a 30-minute intravenous infusion. Following the initial administration, ORENCIA should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter. Any unused portions in the vials must be immediately discarded.

Subcutaneous Dosing Regimen

The safety and efficacy of subcutaneous ORENCIA injection has not been studied in patients under 18 years of age.

2.3 Preparation and Administration Instructions for Intravenous Infusion

Use aseptic technique.

ORENCIA is provided as a lyophilized powder in preservative-free, single-use vials. Each ORENCIA vial provides 250 mg of abatacept for administration. The ORENCIA powder in each vial must be reconstituted with 10 mL of Sterile Water for Injection, USP, using *only the silicone-free disposable syringe provided with each vial* and an 18- to 21-gauge needle. After reconstitution, the concentration of abatacept in the vial will be 25 mg/mL. If the ORENCIA powder is accidentally reconstituted using a siliconized syringe, the solution may develop a few translucent particles. Discard any solutions prepared using siliconized syringes.

If the *silicone-free disposable syringe* is dropped or becomes contaminated, use a new *silicone-free disposable syringe* from inventory. For information on obtaining additional *silicone-free disposable syringes*, contact Bristol-Myers Squibb 1-800-ORENCIA.

1) Use 10 mL of Sterile Water for Injection, USP to reconstitute the ORENCIA powder. To reconstitute the ORENCIA powder, remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Rotate the vial with gentle swirling to minimize foam formation, until the contents are completely dissolved. Do not shake. Avoid prolonged or vigorous agitation.

2) Upon complete dissolution of the lyophilized powder, the vial should be vented with a needle to dissipate any foam that may be present. After reconstitution, each milliliter will contain 25 mg (250 mg/10 mL). The solution should be clear and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.

3) The reconstituted ORENCIA solution must be further diluted to 100 mL as follows. From a 100 mL infusion bag or bottle, withdraw a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of the reconstituted ORENCIA solution required for the patient's dose. Slowly add the reconstituted ORENCIA solution into the infusion bag or bottle using the same *silicone-free disposable syringe provided with each vial*. Gently mix. *Do not shake the bag or bottle*. The final concentration of abatacept in the bag or bottle will depend upon the amount of drug added, but will be no more than 10 mg/mL. Any unused portions in the vials must be immediately discarded.

4) Prior to administration, the ORENCIA solution should be inspected visually for particulate matter and discoloration. Discard the solution if any particulate matter or discoloration is observed.

5) The entire, fully diluted ORENCIA solution should be administered over a period of 30 minutes and must be administered with an infusion set and a *sterile, non-pyrogenic, low-protein-binding filter* (pore size of 0.2 μm to 1.2 μm).

6) The infusion of the fully diluted ORENCIA solution must be completed within 24 hours of reconstitution of the ORENCIA vials. The fully diluted ORENCIA solution may be stored at room temperature or refrigerated at 2ºC to 8ºC (36ºF to 46ºF) before use. Discard the fully diluted solution if not administered within 24 hours.

7) ORENCIA should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of ORENCIA with other agents.

2.4 General Considerations for Subcutaneous Administration

ORENCIA Injection, 125 mg/syringe is not intended for intravenous infusion.

ORENCIA Injection is intended for use under the guidance of a physician or healthcare practitioner. After proper training in subcutaneous injection technique, a patient may self-inject with ORENCIA if a physician/healthcare practitioner determines that it is appropriate. Patients should be instructed to follow the directions provided in the Instructions for Use for additional details on medication administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use ORENCIA prefilled syringes exhibiting particulate matter or discoloration. ORENCIA should be clear and colorless to pale yellow.

Patients using ORENCIA for subcutaneous administration should be instructed to inject the full amount in the syringe (1 mL), which provides 125 mg of ORENCIA, according to the directions provided in the Instructions for Use.

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red, or hard.

3 DOSAGE FORMS AND STRENGTHS

- **Lyophilized Powder for Intravenous Infusion**

  250 mg single-use vial

- **Solution for Subcutaneous Injection**

  125 mg/mL single-dose prefilled glass syringe

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Concomitant Use with TNF Antagonists

In controlled clinical trials in patients with adult RA, patients receiving concomitant intravenous ORENCIA and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively) [*see Adverse Reactions (6.1)*]. These trials failed to demonstrate an important enhancement of efficacy with concomitant administration of ORENCIA with TNF antagonist; therefore, concurrent therapy with ORENCIA and a TNF antagonist is not recommended. While transitioning from TNF antagonist therapy to ORENCIA therapy, patients should be monitored for signs of infection.

5.2 Hypersensitivity

In clinical trials of 2688 adult RA patients treated with intravenous ORENCIA, there were two cases (<0.1%) of anaphylaxis or anaphylactoid reactions. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients. Of the 190 patients with juvenile idiopathic arthritis treated with ORENCIA in clinical trials, there was one case of a hypersensitivity reaction (0.5%). Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction [*see Adverse Reactions (6.1, 6.3)*]. Anaphylaxis or anaphylactoid reactions can occur after the first infusion and can be life threatening. In postmarketing experience, a case of fatal anaphylaxis following the first infusion of ORENCIA has been reported. If an anaphylactic or other serious allergic reaction occurs, administration of ORENCIA should be stopped immediately with appropriate therapy instituted, and the use of ORENCIA should be permanently discontinued.

5.3 Infections

Serious infections, including sepsis and pneumonia, have been reported in patients receiving ORENCIA. Some of these infections have been fatal. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy which in addition to their underlying disease, could further predispose them to infection. Physicians should exercise caution when considering the use of ORENCIA in patients with a history of recurrent infections, underlying conditions which may predispose them to infections, or chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment with ORENCIA should be monitored closely. Administration of ORENCIA should be discontinued if a patient develops a serious infection [*see Adverse Reactions (6.1)*]. A higher rate of serious infections has been observed in adult RA patients treated with concurrent TNF antagonists and ORENCIA [*see Warnings and Precautions (5.1)*].

Prior to initiating immunomodulatory therapies, including ORENCIA, patients should be screened for latent tuberculosis infection with a tuberculin skin test. ORENCIA has not been studied in patients with a positive tuberculosis screen, and the safety of ORENCIA in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculosis screening should be treated by standard medical practice prior to therapy with ORENCIA.

Antirheumatic therapies have been associated with hepatitis B reactivation. Therefore, screening for viral hepatitis should be performed in accordance with published guidelines before starting therapy with ORENCIA. In clinical studies with ORENCIA, patients who screened positive for hepatitis were excluded from study.

5.4 Immunizations

Live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ORENCIA. The efficacy of vaccination in patients receiving ORENCIA is not known. Based on its mechanism of action, ORENCIA may blunt the effectiveness of some immunizations.

It is recommended that patients with juvenile idiopathic arthritis be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ORENCIA therapy.

5.5 Use in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Adult COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea. Use of ORENCIA in patients with RA and COPD should be undertaken with caution and such patients should be monitored for worsening of their respiratory status [*see Adverse Reactions (6.1)*].

5.6 Immunosuppression

The possibility exists for drugs inhibiting T cell activation, including ORENCIA, to affect host defenses against infections and malignancies since T cells mediate cellular immune responses. The impact of treatment with ORENCIA on the development and course of malignancies is not fully understood [*see Adverse Reactions (6.1)*]. In clinical trials in patients with adult RA, a higher rate of infections was seen in ORENCIA-treated patients compared to placebo [*see Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience in Adult RA Patients Treated with Intravenous ORENCIA

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The data described herein reflect exposure to ORENCIA administered intravenously in patients with active RA in placebo-controlled studies (1955 patients with ORENCIA, 989 with placebo). The studies had either a double-blind, placebo-controlled period of 6 months (258 patients with ORENCIA, 133 with placebo) or 1 year (1697 patients with ORENCIA, 856 with placebo). A subset of these patients received concomitant biologic DMARD therapy, such as a TNF blocking agent (204 patients with ORENCIA, 134 with placebo).

The majority of patients in RA clinical studies received one or more of the following concomitant medications with ORENCIA: methotrexate, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, TNF blocking agents, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide, sulfasalazine, and anakinra.

The most serious adverse reactions were serious infections and malignancies.

The most commonly reported adverse events (occurring in ≥10% of patients treated with ORENCIA) were headache, upper respiratory tract infection, nasopharyngitis, and nausea.

The adverse events most frequently resulting in clinical intervention (interruption or discontinuation of ORENCIA) were due to infection. The most frequently reported infections resulting in dose interruption were upper respiratory tract infection (1.0%), bronchitis (0.7%), and herpes zoster (0.7%). The most frequent infections resulting in discontinuation were pneumonia (0.2%), localized infection (0.2%), and bronchitis (0.1%).

Infections

In the placebo-controlled trials, infections were reported in 54% of ORENCIA-treated patients and 48% of placebo-treated patients. The most commonly reported infections (reported in 5%-13% of patients) were upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, influenza, and bronchitis. Other infections reported in fewer than 5% of patients at a higher frequency (>0.5%) with ORENCIA compared to placebo, were rhinitis, herpes simplex, and pneumonia [*see Warnings and Precautions (5.3)*].

Serious infections were reported in 3.0% of patients treated with ORENCIA and 1.9% of patients treated with placebo. The most common (0.2%-0.5%) serious infections reported with ORENCIA were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis [*see Warnings and Precautions (5.3)*].

Malignancies

In the placebo-controlled portions of the clinical trials (1955 patients treated with ORENCIA for a median of 12 months), the overall frequencies of malignancies were similar in the ORENCIA- and placebo-treated patients (1.3% and 1.1%, respectively). However, more cases of lung cancer were observed in ORENCIA-treated patients (4, 0.2%) than placebo-treated patients (0). In the cumulative ORENCIA clinical trials (placebo-controlled and uncontrolled, open-label) a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 4 lymphomas (0.10 cases per 100 patient-years) were observed in 2688 patients (3827 patient-years). The rate observed for lymphoma is approximately 3.5-fold higher than expected in an age- and gender-matched general population based on the National Cancer Institute's Surveillance, Epidemiology, and End Results Database. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. Other malignancies included skin, breast, bile duct, bladder, cervical, endometrial, lymphoma, melanoma, myelodysplastic syndrome, ovarian, prostate, renal, thyroid, and uterine cancers [*see Warnings and Precautions (5.6)*]. The potential role of ORENCIA in the development of malignancies in humans is unknown.

Infusion-Related Reactions and Hypersensitivity Reactions

Acute infusion-related events (adverse reactions occurring within 1 hour of the start of the infusion) in Studies III, IV, and V [*see Clinical Studies (14.1)*] were more common in the ORENCIA-treated patients than the placebo patients (9% for ORENCIA, 6% for placebo). The most frequently reported events (1%-2%) were dizziness, headache, and hypertension.

Acute infusion-related events that were reported in >0.1% and ≤1% of patients treated with ORENCIA included cardiopulmonary symptoms, such as hypotension, increased blood pressure, and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, and wheezing. Most of these reactions were mild (68%) to moderate (28%). Fewer than 1% of ORENCIA-treated patients discontinued due to an acute infusion-related event. In controlled trials, 6 ORENCIA-treated patients compared to 2 placebo-treated patients discontinued study treatment due to acute infusion-related events.

In clinical trials of 2688 adult RA patients treated with intravenous ORENCIA, there were two cases (<0.1%) of anaphylaxis or anaphylactoid reactions. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of ORENCIA-treated patients and generally occurred within 24 hours of ORENCIA infusion. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction [*see Warnings and Precautions (5.2)*].

Adverse Reactions in Patients with COPD

In Study V [*see Clinical Studies (14.1)*], there were 37 patients with chronic obstructive pulmonary disease (COPD) who were treated with ORENCIA and 17 COPD patients who were treated with placebo. The COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo (97% vs 88%, respectively). Respiratory disorders occurred more frequently in ORENCIA-treated patients compared to placebo-treated patients (43% vs 24%, respectively) including COPD exacerbation, cough, rhonchi, and dyspnea. A greater percentage of ORENCIA-treated patients developed a serious adverse event compared to placebo-treated patients (27% vs 6%), including COPD exacerbation (3 of 37 patients [8%]) and pneumonia (1 of 37 patients [3%]) [*see Warnings and Precautions (5.5)*].

Other Adverse Reactions

Adverse events occurring in 3% or more of patients and at least 1% more frequently in ORENCIA-treated patients during placebo-controlled RA studies are summarized in Table 2.

Table 2: Adverse Events Occurring in 3% or More of Patients and at Least 1% More Frequently in ORENCIA-Treated Patients During Placebo-Controlled RA Studies

Adverse Event (Preferred Term)	ORENCIA (n=1955)[a] Percentage	Placebo (n=989)[b] Percentage
Headache	18	13
Nasopharyngitis	12	9
Dizziness	9	7
Cough	8	7
Back pain	7	6
Hypertension	7	4
Dyspepsia	6	4
Urinary tract infection	6	5
Rash	4	3
Pain in extremity	3	2

[a] Includes 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

[b] Includes 134 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

Immunogenicity

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in RA patients for up to 2 years following repeated treatment with ORENCIA. Thirty-four of 1993 (1.7%) patients developed binding antibodies to the entire abatacept molecule or to the CTLA-4 portion of abatacept. Because trough levels of abatacept can interfere with assay results, a subset analysis was performed. In this analysis it was observed that 9 of 154 (5.8%) patients that had discontinued treatment with ORENCIA for over 56 days developed antibodies.

Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralizing antibodies in a cell-based luciferase reporter assay. Six of 9 (67%) evaluable patients were shown to possess neutralizing antibodies. However, the development of neutralizing antibodies may be underreported due to lack of assay sensitivity.

No correlation of antibody development to clinical response or adverse events was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to abatacept in specific assays. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant

medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to abatacept with the incidence of antibodies to other products may be misleading.

Clinical Experience in Methotrexate-Naive Patients

Study VI was an active-controlled clinical trial in methotrexate-naive patients [*see Clinical Studies (14.1)*]. The safety experience in these patients was consistent with Studies I-V.

6.2 Clinical Experience in Adult RA Patients Treated with Subcutaneous ORENCIA

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Study SC-1 was a randomized, double-blind, double-dummy, non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously (SC) and intravenously (IV) in 1457 subjects with rheumatoid arthritis, receiving background methotrexate, and experiencing an inadequate response to methotrexate (MTX-IR) [*see Clinical Studies (14.1)*]. The safety experience and immunogenicity for ORENCIA administered subcutaneously was consistent with intravenous Studies I-VI. Due to the route of administration, injection site reactions and immunogenicity were evaluated in Study SC-1 and two other smaller studies discussed in the sections below.

Injection Site Reactions in Adult RA Patients Treated with Subcutaneous ORENCIA

Study SC-1 compared the safety of abatacept including injection site reactions following subcutaneous or intravenous administration. The overall frequency of injection site reactions was 2.6% (19/736) and 2.5% (18/721) for the subcutaneous abatacept group and the intravenous abatacept group (subcutaneous placebo), respectively. All these injection site reactions (including hematoma, pruritus, and erythema) were mild (83%) to moderate (17%) in severity, and none necessitated drug discontinuation.

Immunogenicity in Adult RA Patients Treated with Subcutaneous ORENCIA

Study SC-1 compared the immunogenicity to abatacept following subcutaneous or intravenous administration. The overall immunogenicity frequency to abatacept was 1.1% (8/725) and 2.3% (16/710) for the subcutaneous and intravenous groups, respectively. The rate is consistent with

previous experience, and there was no correlation of immunogenicity with effects on pharmacokinetics, safety, or efficacy.

Immunogenicity and Safety of Subcutaneous ORENCIA Administration as Monotherapy without an Intravenous Loading Dose

Study SC-2 was conducted to determine the effect of monotherapy use of ORENCIA on immunogenicity following subcutaneous administration without an intravenous load in 100 RA patients, who had not previously received abatacept or other CTLA4Ig, who received either subcutaneous ORENCIA plus methotrexate (n=51) or subcutaneous ORENCIA monotherapy (n=49). No patients in either group developed anti-product antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other subcutaneous studies.

Immunogenicity and Safety of Subcutaneous ORENCIA upon Withdrawal (Three Months) and Restart of Treatment

Study SC-3 in the subcutaneous program was conducted to investigate the effect of withdrawal (three months) and restart of ORENCIA subcutaneous treatment on immunogenicity in RA patients treated concomitantly with methotrexate. One hundred sixty-seven patients were enrolled in the first 3-month treatment period and responders (n=120) were randomized to either subcutaneous ORENCIA or placebo for the second 3-month period (withdrawal period). Patients from this period then received open-label ORENCIA treatment in the final 3-month period of the study (period 3). At the end of the withdrawal period, 0/38 patients who continued to receive subcutaneous ORENCIA developed anti-product antibodies compared to 7/73 (9.6%) of patients who had subcutaneous ORENCIA withdrawn during this period. Half of the patients receiving subcutaneous placebo during the withdrawal period received a single intravenous infusion of ORENCIA at the start of period 3 and half received intravenous placebo. At the end of period 3, when all patients again received subcutaneous ORENCIA, the immunogenicity rates were 1/38 (2.6%) in the group receiving subcutaneous ORENCIA throughout, and 2/73 (2.7%) in the group that had received placebo during the withdrawal period. Upon reinitiating therapy, there were no injection reactions and no differences in response to therapy in patients who were withdrawn from subcutaneous therapy for up to 3 months relative to those who remained on subcutaneous therapy, whether therapy was reintroduced with or without an intravenous loading dose. The safety observed in this study was consistent with that observed in the other studies.

6.3 Clinical Studies Experience in Juvenile Idiopathic Arthritis

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In general, the adverse events in pediatric patients were similar in frequency and type to those seen in adult patients [*see Warnings and Precautions (5), Adverse Reactions (6)*].

ORENCIA has been studied in 190 pediatric patients, 6 to 17 years of age, with polyarticular juvenile idiopathic arthritis. Overall frequency of adverse events in the 4-month, lead-in, open-label period of the study was 70%; infections occurred at a frequency of 36% [*see Clinical Studies (14.2)*]. The most common infections were upper respiratory tract infection and nasopharyngitis. The infections resolved without sequelae, and the types of infections were consistent with those commonly seen in outpatient pediatric populations. Other events that occurred at a prevalence of at least 5% were headache, nausea, diarrhea, cough, pyrexia, and abdominal pain.

A total of 6 serious adverse events (acute lymphocytic leukemia, ovarian cyst, varicella infection, disease flare [2], and joint wear) were reported during the initial 4 months of treatment with ORENCIA.

Of the 190 patients with juvenile idiopathic arthritis treated with ORENCIA in clinical trials, there was one case of a hypersensitivity reaction (0.5%). During Periods A, B, and C, acute infusion-related reactions occurred at a frequency of 4%, 2%, and 3%, respectively, and were consistent with the types of events reported in adults.

Upon continued treatment in the open-label extension period, the types of adverse events were similar in frequency and type to those seen in adult patients, except for a single patient diagnosed with multiple sclerosis while on open-label treatment.

Immunogenicity

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in patients with juvenile idiopathic arthritis following repeated treatment with ORENCIA throughout the open-label period. For patients who were withdrawn from therapy for up to 6 months during the double-blind period, the rate of antibody formation to the CTLA-4 portion of the molecule was 41% (22/54), while for those who remained on therapy the rate was 13% (7/54). Twenty of these patients had samples that could be tested for antibodies

with neutralizing activity; of these, 8 (40%) patients were shown to possess neutralizing antibodies.

The presence of antibodies was generally transient and titers were low. The presence of antibodies was not associated with adverse events, changes in efficacy, or an effect on serum concentrations of abatacept. For patients who were withdrawn from ORENCIA during the double-blind period for up to 6 months, no serious acute infusion-related events were observed upon re-initiation of ORENCIA therapy.

6.4 Postmarketing Experience

Adverse reactions have been reported during the postapproval use of ORENCIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ORENCIA. Based on the postmarketing experience in adult RA patients, the following adverse reaction has been identified during postapproval use with ORENCIA.

- Vasculitis (including cutaneous vasculitis and leukocytoclastic vasculitis)

7 DRUG INTERACTIONS

7.1 TNF Antagonists

Concurrent administration of a TNF antagonist with ORENCIA has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone. Concurrent therapy with ORENCIA and TNF antagonists is not recommended [*see Warnings and Precautions (5.1)*].

7.2 Other Biologic RA Therapy

There is insufficient experience to assess the safety and efficacy of ORENCIA administered concurrently with other biologic RA therapy, such as anakinra, and therefore such use is not recommended.

7.3 Blood Glucose Testing

Parenteral drug products containing maltose can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ). The GDH-PQQ based glucose monitoring systems may react with the maltose present in ORENCIA for intravenous administration, resulting in falsely elevated blood glucose readings on the day of infusion. When receiving ORENCIA through intravenous administration, patients

that require blood glucose monitoring should be advised to consider methods that do not react with maltose, such as those based on glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods.

ORENCIA for subcutaneous administration does not contain maltose; therefore, patients do not need to alter their glucose monitoring.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of ORENCIA use in pregnant women. Abatacept has been shown to cross the placenta in animals, and in animal reproduction studies alterations in immune function occurred. ORENCIA should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Abatacept was not teratogenic when administered to pregnant mice at doses up to 300 mg/kg and in pregnant rats and rabbits at doses up to 200 mg/kg daily representing approximately 29 times the exposure associated with the maximum recommended human dose (MRHD) of 10 mg/kg based on AUC (area under the time-concentration curve).

Abatacept administered to female rats every three days during early gestation and throughout the lactation period, produced no adverse effects in offspring at doses up to 45 mg/kg, representing 3 times the exposure associated with the MRHD of 10 mg/kg based on AUC. However, at 200 mg/kg, 11 times the MRHD exposure, alterations in immune function were observed consisting of a 9-fold increase in T-cell dependent antibody response in female pups and thyroid inflammation in one female pup. It is not known whether these findings indicate a risk for development of autoimmune diseases in humans exposed *in utero* to abatacept. However, exposure to abatacept in the juvenile rat, which may be more representative of the fetal immune system state in the human, resulted in immune system abnormalities including inflammation of the thyroid and pancreas [*see Nonclinical Toxicology (13.2)*].

Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to ORENCIA, a pregnancy registry has been established. Healthcare professionals are encouraged to register patients and pregnant women are encouraged to enroll themselves by calling 1-877-311-8972.

8.3 Nursing Mothers

It is not known whether ORENCIA is excreted into human milk or absorbed systemically after ingestion by a nursing infant. However, abatacept was excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ORENCIA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Intravenous ORENCIA is indicated for reducing signs and symptoms in pediatric patients with moderately to severely active polyarticular juvenile idiopathic arthritis ages 6 years and older. ORENCIA may be used as monotherapy or concomitantly with methotrexate.

Studies in juvenile rats exposed to ORENCIA prior to immune system maturity have shown immune system abnormalities including an increase in the incidence of infections leading to death as well as inflammation of the thyroid and pancreas [*see Nonclinical Toxicology (13.2)*]. Studies in adult mice and monkeys have not demonstrated similar findings. As the immune system of the rat is undeveloped in the first few weeks after birth, the relevance of these results to humans greater than 6 years of age (where the immune system is largely developed) is unknown.

ORENCIA is not recommended for use in patients below the age of 6 years.

The safety and effectiveness of ORENCIA in pediatric patients below 6 years of age have not been established. The safety and efficacy of ORENCIA in pediatric patients for uses other than juvenile idiopathic arthritis have not been established.

The safety and efficacy of subcutaneous ORENCIA has not been studied in patients under 18 years of age.

8.5 Geriatric Use

A total of 323 patients 65 years of age and older, including 53 patients 75 years and older, received ORENCIA in clinical studies. No overall differences in safety or effectiveness were observed between these patients and younger patients, but these numbers are too low to rule out differences. The frequency of serious infection and malignancy among ORENCIA-treated patients over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

10 OVERDOSAGE

Doses up to 50 mg/kg have been administered intravenously without apparent toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

11 DESCRIPTION

ORENCIA® (abatacept) is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant DNA technology in a mammalian cell expression system. The apparent molecular weight of abatacept is 92 kilodaltons.

ORENCIA lyophilized powder for intravenous infusion is supplied as a sterile, white, preservative-free, lyophilized powder for intravenous administration. Following reconstitution of the lyophilized powder with 10 mL of Sterile Water for Injection, USP, the solution of ORENCIA is clear, colorless to pale yellow, with a pH range of 7.2 to 7.8. Each single-use vial of ORENCIA provides 250 mg abatacept, maltose (500 mg), monobasic sodium phosphate (17.2 mg), and sodium chloride (14.6 mg) for administration.

ORENCIA solution for subcutaneous administration is supplied as a sterile, preservative-free, clear, colorless to pale-yellow solution with a pH of 6.8 to 7.4. Each single dose of subcutaneous injection provides 125 mg abatacept, dibasic sodium phosphate anhydrous (0.838 mg), monobasic sodium phosphate monohydrate (0.286 mg), poloxamer 188 (8 mg), sucrose (170 mg), and quantity sufficient to 1 mL with water for injection. Unlike the intravenous formulation, ORENCIA solution for subcutaneous administration contains no maltose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abatacept, a selective costimulation modulator, inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes. Activated T lymphocytes are implicated in the pathogenesis of RA and are found in the synovium of patients with RA.

In vitro, abatacept decreases T cell proliferation and inhibits the production of the cytokines TNF alpha (TNFα), interferon-γ, and interleukin-2. In a rat collagen-induced arthritis model, abatacept suppresses inflammation, decreases anti-collagen antibody production, and reduces antigen

specific production of interferon-γ. The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its effects in RA is unknown.

12.2 Pharmacodynamics

In clinical trials with ORENCIA at doses approximating 10 mg/kg, decreases were observed in serum levels of soluble interleukin-2 receptor (sIL-2R), interleukin-6 (IL-6), rheumatoid factor (RF), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP3), and TNFα. The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its effects in RA is unknown.

12.3 Pharmacokinetics

Healthy Adults and Adult RA - Intravenous Administration

The pharmacokinetics of abatacept were studied in healthy adult subjects after a single 10 mg/kg intravenous infusion and in RA patients after multiple 10 mg/kg intravenous infusions (see Table 3).

Table 3: Pharmacokinetic Parameters (Mean, Range) in Healthy Subjects and RA Patients After 10 mg/kg Intravenous Infusion(s)

PK Parameter	Healthy Subjects (After 10 mg/kg Single Dose) n=13	RA Patients (After 10 mg/kg Multiple Doses[a]) n=14
Peak Concentration (C_{max}) [mcg/mL]	292 (175-427)	295 (171-398)
Terminal half-life ($t_{1/2}$) [days]	16.7 (12-23)	13.1 (8-25)
Systemic clearance (CL) [mL/h/kg]	0.23 (0.16-0.30)	0.22 (0.13-0.47)
Volume of distribution (Vss) [L/kg]	0.09 (0.06-0.13)	0.07 (0.02-0.13)

[a] Multiple intravenous infusions were administered at days 1, 15, 30, and monthly thereafter.

The pharmacokinetics of abatacept in RA patients and healthy subjects appeared to be comparable. In RA patients, after multiple intravenous infusions, the pharmacokinetics of abatacept showed proportional increases of C_{max} and AUC over the dose range of 2 mg/kg to 10 mg/kg. At 10 mg/kg, serum concentration appeared to reach a steady-state by day 60 with a mean (range) trough concentration of 24 mcg/mL (1 to 66 mcg/mL). No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in RA patients.

Population pharmacokinetic analyses in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for

body weight) did not affect clearance. Concomitant methotrexate, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance.

No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept.

Juvenile Idiopathic Arthritis

In patients 6 to 17 years of age, the mean (range) steady-state serum peak and trough concentrations of abatacept were 217 mcg/mL (57 to 700 mcg/mL) and 11.9 mcg/mL (0.15 to 44.6 mcg/mL). Population pharmacokinetic analyses of the serum concentration data showed that clearance of abatacept increased with baseline body weight. The estimated mean (range) clearance of abatacept in the juvenile idiopathic arthritis patients was 0.4 mL/h/kg (0.20 to 1.12 mL/h/kg). After accounting for the effect of body weight, the clearance of abatacept was not related to age and gender. Concomitant methotrexate, corticosteroids, and NSAIDs were also shown not to influence abatacept clearance.

Adult RA - Subcutaneous Administration

Abatacept exhibited linear pharmacokinetics following subcutaneous administration. The mean (range) for C_{min} and C_{max} at steady state observed after 85 days of treatment was 32.5 mcg/mL (6.6 to 113.8 mcg/mL) and 48.1 mcg/mL (9.8 to 132.4 mcg/mL), respectively. The bioavailability of abatacept following subcutaneous administration relative to intravenous administration is 78.6%. Mean estimates for systemic clearance (0.28 mL/h/kg), volume of distribution (0.11 L/kg), and terminal half-life (14.3 days) were comparable between subcutaneous and intravenous administration.

Study SC-2 was conducted to determine the effect of monotherapy use of ORENCIA on immunogenicity following subcutaneous administration without an intravenous load. When the intravenous loading dose was not administered, a mean trough concentration of 12.6 mcg/mL was achieved after 2 weeks of dosing.

Consistent with the intravenous data, population pharmacokinetic analyses for subcutaneous abatacept in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate, corticosteroids, and NSAIDs, did not influence abatacept apparent clearance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a mouse carcinogenicity study, weekly subcutaneous injections of 20, 65, or 200 mg/kg of abatacept administered for up to 84 weeks in males and 88 weeks in females were associated with increases in the incidence of malignant lymphomas (all doses) and mammary gland tumors (intermediate- and high-dose in females). The mice from this study were infected with murine leukemia virus and mouse mammary tumor virus. These viruses are associated with an increased incidence of lymphomas and mammary gland tumors, respectively, in immunosuppressed mice. The doses used in these studies produced exposures 0.8, 2.0, and 3.0 times higher, respectively, than the exposure associated with the maximum recommended human dose (MRHD) of 10 mg/kg based on AUC (area under the time-concentration curve). The relevance of these findings to the clinical use of ORENCIA is unknown.

In a one-year toxicity study in cynomolgus monkeys, abatacept was administered intravenously once weekly at doses up to 50 mg/kg (producing 9 times the MRHD exposure based on AUC). Abatacept was not associated with any significant drug-related toxicity. Reversible pharmacological effects consisted of minimal transient decreases in serum IgG and minimal to severe lymphoid depletion of germinal centers in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic morphologic changes was observed, despite the presence of a virus (lymphocryptovirus) known to cause these lesions in immunosuppressed monkeys within the time frame of this study. The relevance of these findings to the clinical use of ORENCIA is unknown.

No mutagenic potential of abatacept was observed in the *in vitro* bacterial reverse mutation (Ames) or Chinese hamster ovary/hypoxanthine guanine phosphoribosyl-transferase (CHO/HGPRT) forward point mutation assays with or without metabolic activation, and no chromosomal aberrations were observed in human lymphocytes treated with abatacept with or without metabolic activation.

Abatacept had no adverse effects on male or female fertility in rats at doses up to 200 mg/kg every three days (11 times the MRHD exposure based on AUC).

13.2 Animal Toxicology and/or Pharmacology

A juvenile animal study was conducted in rats dosed with abatacept from 4 to 94 days of age in which an increase in the incidence of infections leading to death occurred at all doses compared with controls. Altered T-cell subsets including increased T-helper cells and reduced T-regulatory cells were observed. In addition, inhibition of T-cell-dependent antibody responses (TDAR) was

observed. Upon following these animals into adulthood, lymphocytic inflammation of the thyroid and pancreatic islets was observed.

In studies of adult mice and monkeys, inhibition of TDAR was apparent. However, infection and mortality, altered T-helper cells, and inflammation of thyroid and pancreas were not observed.

14 CLINICAL STUDIES

14.1 Adult Rheumatoid Arthritis

The efficacy and safety of ORENCIA for intravenous administration were assessed in six randomized, double-blind, controlled studies (five placebo-controlled and one active-controlled) in patients ≥18 years of age with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Studies I, II, III, IV, and VI required patients to have at least 12 tender and 10 swollen joints at randomization. Study V did not require any specific number of tender or swollen joints. ORENCIA or placebo treatment was given intravenously at weeks 0, 2, and 4 and then every 4 weeks thereafter in intravenous Studies I, II, III, IV, and VI. The safety and efficacy of ORENCIA for subcutaneous administration were assessed in Study SC-1, which was a randomized, double-blind, double-dummy, non-inferiority study that compared abatacept administered subcutaneously and intravenously in 1457 subjects with rheumatoid arthritis (RA), receiving background methotrexate (MTX), and experiencing an inadequate response to methotrexate (MTX-IR).

Study I evaluated ORENCIA as monotherapy in 122 patients with active RA who had failed at least one non-biologic DMARD or etanercept. In Study II and Study III, the efficacy and safety of ORENCIA were assessed in patients with an inadequate response to methotrexate and who were continued on their stable dose of methotrexate. In Study IV, the efficacy and safety of ORENCIA were assessed in patients with an inadequate response to a TNF blocking agent, with the TNF blocking agent discontinued prior to randomization; other DMARDs were permitted. Study V primarily assessed safety in patients with active RA requiring additional intervention in spite of current therapy with DMARDs; all DMARDs used at enrollment were continued. Patients in Study V were not excluded for comorbid medical conditions. In Study VI, the efficacy and safety of ORENCIA were assessed in methotrexate-naive patients with RA of less than 2 years disease duration. In Study VI, patients previously naive to methotrexate were randomized to receive ORENCIA plus methotrexate or methotrexate plus placebo. In Study SC-1, the goal was to demonstrate the efficacy and safety of ORENCIA subcutaneous relative to ORENCIA intravenous administration in subjects with moderate to severely active RA and experiencing inadequate response to methotrexate, using a non-inferiority study design.

Study I patients were randomized to receive one of three doses of ORENCIA (0.5, 2, or 10 mg/kg) or placebo ending at week 8. Study II patients were randomized to receive ORENCIA 2 or 10 mg/kg or placebo for 12 months. Study III, IV, V, and VI patients were randomized to receive a dose of ORENCIA based on weight range or placebo for 12 months (Studies III, V, and VI) or 6 months (Study IV). The dose of ORENCIA was 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1000 mg for patients weighing greater than 100 kg. In Study SC-1, patients were randomized with stratification by body weight (<60 kg, 60 to 100 kg, >100 kg) to receive ORENCIA 125 mg subcutaneous injections weekly, after a single intravenous loading dose of ORENCIA based on body weight or ORENCIA intravenously on Days 1, 15, 29, and every four weeks thereafter. Subjects continued taking their current dose of methotrexate from the day of randomization.

Clinical Response

The percent of ORENCIA-treated patients achieving ACR 20, 50, and 70 responses and major clinical response in Studies I, III, IV, and VI are shown in Table 4. ORENCIA-treated patients had higher ACR 20, 50, and 70 response rates at 6 months compared to placebo-treated patients. Month 6 ACR response rates in Study II for the 10 mg/kg group were similar to the ORENCIA group in Study III.

In Studies III and IV, improvement in the ACR 20 response rate versus placebo was observed within 15 days in some patients and within 29 days versus methotrexate in Study VI. In Studies II, III, and VI, ACR response rates were maintained to 12 months in ORENCIA-treated patients. ACR responses were maintained up to three years in the open-label extension of Study II. In Study III, ORENCIA-treated patients experienced greater improvement than placebo-treated patients in morning stiffness.

In Study VI, a greater proportion of patients treated with ORENCIA plus methotrexate achieved a low level of disease activity as measured by a DAS28-CRP less than 2.6 at 12 months compared to those treated with methotrexate plus placebo (Table 4). Of patients treated with ORENCIA plus methotrexate who achieved DAS28-CRP less than 2.6, 54% had no active joints, 17% had one active joint, 7% had two active joints, and 22% had three or more active joints, where an active joint was a joint that was rated as tender or swollen or both.

In Study SC-1, the main outcome measure was ACR 20 at 6 months. The pre-specified non-inferiority margin was a treatment difference of −7.5%. As shown in Table 4, the study demonstrated non-inferiority of ORENCIA administered subcutaneously to intravenous infusions of ORENCIA with respect to ACR 20 responses up to 6 months of treatment. ACR 50 and 70 responses are also shown in Table 4. No major differences in ACR responses were observed

between intravenous and subcutaneous treatment groups in subgroups based on weight categories (less than 60 kg, 60 to 100 kg, and more than 100 kg; data not shown).

Table 4: Clinical Responses in Controlled Trials

	Percent of Patients									
	Intravenous Administration								Subcutaneous Administration	
	Inadequate Response to DMARDs		Inadequate Response to Methotrexate (MTX)		Inadequate Response to TNF Blocking Agent		MTX-Naive		Inadequate Response to MTX	
	Study I		Study III		Study IV		Study VI		Study SC-1	
Response Rate	ORN[a] n=32	PBO n=32	ORN[b] +MTX n=424	PBO +MTX n=214	ORN[b] + DMARDs n=256	PBO + DMARDs n=133	ORN[b] +MTX n=256	PBO +MTX n=253	ORN[e] SC +MTX n=693	ORN[e] IV +MTX n=678
ACR 20										
Month 3	53%	31%	62%‡	37%	46%‡	18%	64%*	53%	68%	69%
Month 6	NA	NA	68%‡	40%	50%‡	20%	75%†	62%	76%§	76%
Month 12	NA	NA	73%‡	40%	NA	NA	76%‡	62%	NA	NA
ACR 50										
Month 3	16%	6%	32%‡	8%	18%†	6%	40%‡	23%	33%	39%
Month 6	NA	NA	40%‡	17%	20%‡	4%	53%‡	38%	52%	50%
Month 12	NA	NA	48%‡	18%	NA	NA	57%‡	42%	NA	NA
ACR 70										
Month 3	6%	0	13%‡	3%	6%*	1%	19%†	10%	13%	16%
Month 6	NA	NA	20%‡	7%	10%†	2%	32%†	20%	26%	25%
Month 12	NA	NA	29%‡	6%	NA	NA	43%‡	27%	NA	NA
Major Clinical Response[c]	NA	NA	14%‡	2%	NA	NA	27%‡	12%	NA	NA
DAS28-CRP <2.6[d]										
Month 12	NA	NA	NA	NA	NA	NA	41%‡	23%	NA	NA

* p<0.05, ORENCIA (ORN) vs placebo (PBO) or MTX.

† p<0.01, ORENCIA vs placebo or MTX.

‡ p<0.001, ORENCIA vs placebo or MTX.

§ 95% CI: −4.2, 4.8 (based on prespecified margin for non-inferiority of −7.5%).

a 10 mg/kg.

b Dosing based on weight range [*see Dosage and Administration (2.1)*].

c Major clinical response is defined as achieving an ACR 70 response for a continuous 6-month period.

d Refer to text for additional description of remaining joint activity.

e Per protocol data is presented in table. For ITT; n=736, 721 for SC and IV ORENCIA, respectively.

The results of the components of the ACR response criteria for Studies III, IV, and SC-1 are shown in Table 5 (results at Baseline [BL] and 6 months [6 M]). In ORENCIA-treated patients, greater improvement was seen in all ACR response criteria components through 6 and 12 months than in placebo-treated patients.

Table 5: Components of ACR Responses at 6 Months

	Intravenous Administration								**Subcutaneous Administration**			
	Inadequate Response to Methotrexate (MTX)				**Inadequate Response to TNF Blocking Agent**				**Inadequate Response to MTX**			
	Study III				**Study IV**				**Study SC-1[c]**			
	ORN +MTX n=424		PBO +MTX n=214		ORN +DMARDs n=256		PBO +DMARDs n=133		ORN SC +MTX n=693		ORN IV +MTX n=678	
Component (median)	BL	6 M	BL	6 M	BL	6 M	BL	6 M	BL	6 M	BL	6 M
Number of tender joints (0-68)	28	7‡	31	14	30	13‡	31	24	27	5	27	6
Number of swollen joints (0-66)	19	5‡	20	11	21	10‡	20	14	18	4	18	3
Pain[a]	67	27‡	70	50	73	43†	74	64	71	25	70	28
Patient global assessment[a]	66	29‡	64	48	71	44‡	73	63	70	26	68	27
Disability index[b]	1.75	1.13‡	1.75	1.38	1.88	1.38‡	2.00	1.75	1.88	1.00	1.75	1.00
Physician global assessment[a]	69	21‡	68	40	71	32‡	69	54	65	16	65	15
CRP (mg/dL)	2.2	0.9‡	2.1	1.8	3.4	1.3‡	2.8	2.3	1.6	0.7	1.8	0.7

† p<0.01, ORENCIA (ORN) vs placebo (PBO), based on mean percent change from baseline.

‡ p<0.001, ORENCIA vs placebo, based on mean percent change from baseline.

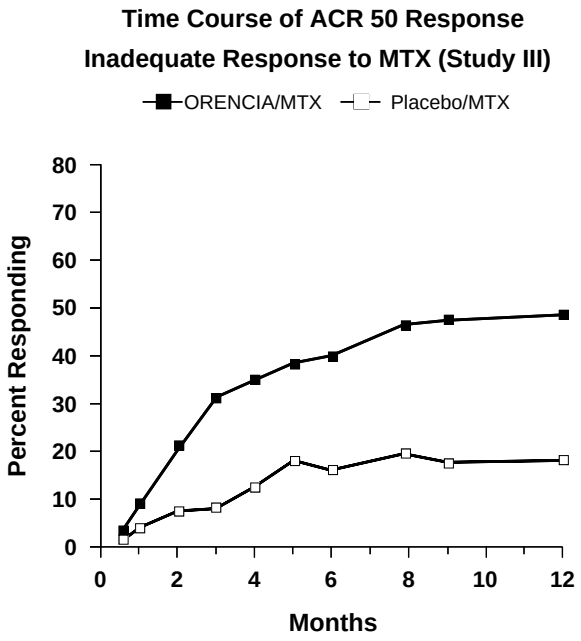
a Visual analog scale: 0 = best, 100 = worst.

b Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

c SC-1 is a non-inferiority study. Per protocol data is presented in table.

The percent of patients achieving the ACR 50 response for Study III by visit is shown in Figure 1. The time course for the ORENCIA group in Study VI was similar to that in Study III.

Figure 1: Percent of Patients Achieving ACR 50 Response by Visit* (Study III)



*The same patients may not have responded at each time point.

The percent of patients achieving the ACR 50 response for Study SC-1 in the ORENCIA subcutaneous (SC) and intravenous (IV) treatment arms at each treatment visit was as follows: Day 15—SC 3%, IV 5%; Day 29—SC 11%, IV 14%; Day 57—SC 24%, IV 30%; Day 85—SC 33%, IV 38%; Day 113—SC 39%, IV 41%; Day 141—SC 46%, IV 47%; Day 169—SC 51%, IV 50%.

Radiographic Response

In Study III and Study VI, structural joint damage was assessed radiographically and expressed as change from baseline in the Genant-modified Total Sharp Score (TSS) and its components, the Erosion Score (ES) and Joint Space Narrowing (JSN) score. ORENCIA/methotrexate slowed the progression of structural damage compared to placebo/methotrexate after 12 months of treatment as shown in Table 6.

Table 6: Mean Radiographic Changes in Study III[a] and Study VI[b]

Parameter	ORENCIA/MTX	Placebo/MTX	Differences	P-value[d]
Study III				
First Year				
TSS	1.07	2.43	1.36	<0.01
ES	0.61	1.47	0.86	<0.01
JSN score	0.46	0.97	0.51	<0.01
Second Year				
TSS	0.48	0.74[c]	-	-
ES	0.23	0.22[c]	-	-
JSN score	0.25	0.51[c]	-	-
Study VI				
First Year				
TSS	0.6	1.1	0.5	0.04

[a] Patients with an inadequate response to MTX.
[b] MTX-naive patients.
[c] Patients received 1 year of placebo/MTX followed by 1 year of ORENCIA/MTX.
[d] Based on a nonparametric ANCOVA model.

In the open-label extension of Study III, 75% of patients initially randomized to ORENCIA/methotrexate and 65% of patients initially randomized to placebo/methotrexate were evaluated radiographically at Year 2. As shown in Table 6, progression of structural damage in ORENCIA/methotrexate-treated patients was further reduced in the second year of treatment.

Following 2 years of treatment with ORENCIA/methotrexate, 51% of patients had no progression of structural damage as defined by a change in the TSS of zero or less compared with baseline. Fifty-six percent (56%) of ORENCIA/methotrexate-treated patients had no progression during the first year compared to 45% of placebo/methotrexate-treated patients. In their second year of treatment with ORENCIA/methotrexate, more patients had no progression than in the first year (65% vs 56%).

Physical Function Response and Health-Related Outcomes

Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI). In the HAQ-DI, ORENCIA demonstrated greater improvement from baseline versus placebo in Studies II-V and versus methotrexate in Study VI. In Study SC-1, improvement from baseline as measured by HAQ-DI at 6 months and over time was similar between subcutaneous and intravenous administration. The results from Studies II and III are shown in Table 7. Similar results were observed in Study V compared to placebo and in

Study VI compared to methotrexate. During the open-label period of Study II, the improvement in physical function has been maintained for up to 3 years.

Table 7: Mean Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

	Inadequate Response to Methotrexate			
	Study II		Study III	
HAQ Disability Index	ORENCIA[a] +MTX (n=115)	Placebo +MTX (n=119)	ORENCIA[b] +MTX (n=422)	Placebo +MTX (n=212)
Baseline (Mean)	0.98[c]	0.97[c]	1.69[d]	1.69[d]
Mean Improvement Year 1	0.40[c],***	0.15[c]	0.66[d],***	0.37[d]

*** p<0.001, ORENCIA vs placebo.

[a] 10 mg/kg.

[b] Dosing based on weight range [*see Dosage and Administration (2.1)*].

[c] Modified Health Assessment Questionnaire: 0 = best, 3 = worst; 8 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

[d] Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Health-related quality of life was assessed by the SF-36 questionnaire at 6 months in Studies II, III, and IV and at 12 months in Studies II and III. In these studies, improvement was observed in the ORENCIA group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

14.2 Juvenile Idiopathic Arthritis

The safety and efficacy of ORENCIA were assessed in a three-part study including an open-label extension in children with polyarticular juvenile idiopathic arthritis (JIA). Patients 6 to 17 years of age (n=190) with moderately to severely active polyarticular JIA who had an inadequate response to one or more DMARDs, such as methotrexate or TNF antagonists, were treated. Patients had a disease duration of approximately 4 years with moderately to severely active disease at study entry, as determined by baseline counts of active joints (mean, 16) and joints with loss of motion (mean, 16); patients had elevated C-reactive protein (CRP) levels (mean, 3.2 mg/dL) and ESR (mean, 32 mm/h). The patients enrolled had subtypes of JIA that at disease onset included Oligoarticular (16%), Polyarticular (64%; 20% were rheumatoid factor positive), and Systemic (20%). At study entry, 74% of patients were receiving methotrexate (mean dose, 13.2 mg/m^2 per week) and remained on a stable dose of methotrexate (those not receiving methotrexate did not initiate methotrexate treatment during the study).

In Period A (open-label, lead-in), patients received 10 mg/kg (maximum 1000 mg per dose) intravenously on days 1, 15, 29, and monthly thereafter. Response was assessed utilizing the ACR Pediatric 30 definition of improvement, defined as ≥30% improvement in at least 3 of the 6 JIA core set variables and ≥30% worsening in not more than 1 of the 6 JIA core set variables. Patients demonstrating an ACR Pedi 30 response at the end of Period A were randomized into the double-blind phase (Period B) and received either ORENCIA or placebo for 6 months or until disease flare. Disease flare was defined as a ≥30% worsening in at least 3 of the 6 JIA core set variables with ≥30% improvement in not more than 1 of the 6 JIA core set variables; ≥2 cm of worsening of the Physician or Parent Global Assessment was necessary if used as 1 of the 3 JIA core set variables used to define flare, and worsening in ≥2 joints was necessary if the number of active joints or joints with limitation of motion was used as 1 of the 3 JIA core set variables used to define flare.

At the conclusion of Period A, pediatric ACR 30/50/70 responses were 65%, 50%, and 28%, respectively. Pediatric ACR 30 responses were similar in all subtypes of JIA studied.

During the double-blind randomized withdrawal phase (Period B), ORENCIA-treated patients experienced significantly fewer disease flares compared to placebo-treated patients (20% vs 53%); 95% CI of the difference (15%, 52%). The risk of disease flare among patients continuing on ORENCIA was less than one-third than that for patients withdrawn from ORENCIA treatment (hazard ratio=0.31, 95% CI [0.16, 0.59]). Among patients who received ORENCIA throughout the study (Period A, Period B, and the open-label extension Period C), the proportion of pediatric ACR 30/50/70 responders has remained consistent for 1 year.

16 HOW SUPPLIED/STORAGE AND HANDLING

For Intravenous Infusion

ORENCIA® (abatacept) lyophilized powder for intravenous infusion is supplied as an individually packaged, single-use vial with a silicone-free disposable syringe, providing 250 mg of abatacept in a 15-mL vial: NDC 0003-2187-10.

For Subcutaneous Injection

ORENCIA® (abatacept) injection solution for subcutaneous administration is supplied either as a single-dose disposable prefilled glass syringe with UltraSafe Passive® needle guard with flange extenders or as a single-dose disposable prefilled glass syringe with flange extender. The Type I glass syringe has a coated stopper and fixed stainless steel needle (5 bevel, 29-gauge thin wall,

½-inch needle) covered with a rigid needle shield. The prefilled syringe provides 125 mg of abatacept in 1 mL and is provided in the following packages:

NDC 0003-2188-11: pack of 4 syringes with a passive needle safety guard

NDC 0003-2188-31: pack of 4 syringes without a passive needle safety guard

Storage

ORENCIA lyophilized powder supplied in a vial should be refrigerated at 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date on the vial. Protect the vials from light by storing in the original package until time of use.

ORENCIA solution supplied in a prefilled syringe should be refrigerated at 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date on the prefilled syringe. Protect from light by storing in the original package until time of use. Do not allow the prefilled syringe to freeze.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

17.1 Concomitant Use With Biologic Medications for RA

Patients should be informed that they should not receive ORENCIA treatment concomitantly with a TNF antagonist, such as adalimumab, etanercept, and infliximab because such combination therapy may increase their risk for infections [*see Indications and Usage (1.3), Warnings and Precautions (5.1),* and *Drug Interactions (7.1)*], and that they should not receive ORENCIA concomitantly with other biologic RA therapy, such as anakinra because there is not enough information to assess the safety and efficacy of such combination therapy [*see Indications and Usage (1.3), Drug Interactions (7.2)*].

17.2 Hypersensitivity

Patients should be instructed to immediately tell their healthcare professional if they experience symptoms of an allergic reaction during or for the first day after the administration of ORENCIA [*see Warnings and Precautions (5.2)*].

17.3 Infections

Patients should be asked if they have a history of recurrent infections, have underlying conditions which may predispose them to infections, or have chronic, latent, or localized infections. Patients should be asked if they have had tuberculosis (TB), a positive skin test for

TB, or recently have been in close contact with someone who has had TB. Patients should be instructed that they may be tested for TB before they receive ORENCIA. Patients should be informed to tell their healthcare professional if they develop an infection during therapy with ORENCIA [*see Warnings and Precautions (5.3)*].

17.4 Immunizations

Patients should be informed that live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation. Caregivers of patients with juvenile idiopathic arthritis should be informed that the patient should be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ORENCIA therapy and to discuss with their healthcare provider how best to handle future immunizations once ORENCIA therapy has been initiated [*see Warnings and Precautions (5.4)*].

17.5 Pregnancy and Nursing Mothers

Patients should be informed that ORENCIA has not been studied in pregnant women or nursing mothers so the effects of ORENCIA on pregnant women or nursing infants are not known. Patients should be instructed to tell their healthcare professional if they are pregnant, become pregnant, or are thinking about becoming pregnant [*see Use in Specific Populations (8.1)*]. Patients should be instructed to tell their healthcare professional if they plan to breastfeed their infant [*see Use in Specific Populations (8.3)*].

17.6 Blood Glucose Testing

Intravenous Administration

Patients should be asked if they have diabetes. Maltose is contained in ORENCIA for intravenous administration and can give falsely elevated blood glucose readings with certain blood glucose monitors on the day of ORENCIA infusion. If a patient is using such a monitor, the patient should be advised to discuss with their healthcare professional methods that do not react with maltose [*see Drug Interactions (7.3)*].

Subcutaneous Administration

ORENCIA for subcutaneous administration does not contain maltose; therefore, patients do not need to alter their glucose monitoring.

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

Rev October 2014

PATIENT INFORMATION

ORENCIA® (oh-REN-see-ah)
(abatacept)
Lyophilized Powder for Intravenous Infusion

ORENCIA® (oh-REN-see-ah)
(abatacept)
Injection, Solution for Subcutaneous Administration

Read this Patient Information before you start using ORENCIA and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ORENCIA?

ORENCIA is a prescription medicine that reduces signs and symptoms in:

- adults with moderate to severe rheumatoid arthritis (RA), including those who have not been helped enough by other medicines for RA. ORENCIA may prevent further damage to your bones and joints and may help your ability to perform daily activities. In adults, ORENCIA may be used alone or with other RA treatments other than tumor necrosis factor (TNF) antagonists.
- children and adolescents 6 years of age and older with moderate to severe polyarticular juvenile idiopathic arthritis (JIA). ORENCIA may be used alone or with methotrexate.

It is not known if ORENCIA is safe and effective in children under 6 years of age.

It is not known if ORENCIA is safe and effective in children for uses other than juvenile idiopathic arthritis.

It is not known if ORENCIA for subcutaneous injection is safe and effective in children under 18 years of age.

What should I tell my healthcare provider before using ORENCIA?

Before you use ORENCIA, tell your healthcare provider if you:

- have any kind of infection even if it is small (such as an open cut or sore), or an infection that is in your whole body (such as the flu). If you have an infection when taking ORENCIA, you may have a higher chance for getting serious side effects.

- have an infection that will not go away or an infection that keeps coming back.
- are allergic to abatacept or any of the ingredients in ORENCIA. See the end of this leaflet for a list of the ingredients in ORENCIA.
- have or have had inflammation of your liver due to an infection (viral hepatitis). Before you use ORENCIA, your healthcare provider may examine you for hepatitis.
- have had a lung infection called tuberculosis (TB), a positive skin test for TB, or you recently have been in close contact with someone who has had TB. Before you use ORENCIA, your healthcare provider may examine you for TB or perform a skin test. Symptoms of TB may include:
    - a cough that does not go away
    - weight loss
    - fever
    - night sweats
- are scheduled to have surgery.
- recently received a vaccination or are scheduled for a vaccination. If you are receiving ORENCIA, and for 3 months after you stop receiving ORENCIA, you should not receive live vaccines.
- have a history of a breathing problem called chronic obstructive pulmonary disease (COPD).
- have diabetes and use a blood glucose monitor to check your blood sugar (blood glucose) levels. ORENCIA for intravenous infusion (given through a needle placed in a vein) contains maltose, a type of sugar that can give false high blood sugar readings with certain types of blood glucose monitors, on the day of ORENCIA infusion. Your doctor may tell you to use a different way to monitor your blood sugar levels.
- ORENCIA for subcutaneous injection (injected under the skin) does not contain maltose. You do not need to change your blood sugar monitoring if you are taking ORENCIA subcutaneously.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if ORENCIA can harm your unborn baby.

  Bristol-Myers Squibb Company has a registry for pregnant women exposed to ORENCIA. The purpose of this registry is to check the health of the pregnant mother and her child. Women are encouraged to call the registry themselves or ask their doctors to contact the registry for them by calling 1-877-311-8972.
- are breastfeeding or plan to breastfeed. It is not known if ORENCIA passes into your breast milk. You and your healthcare provider should decide if you will use ORENCIA or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

ORENCIA may affect the way other medicines work, and other medicines may affect the way ORENCIA works causing serious side effects.

Especially tell your healthcare provider if you take other biologic medicines to treat RA or JIA that may affect your immune system, such as:

- Enbrel® (etanercept)
- Humira® (adalimumab)
- Remicade® (infliximab)
- Kineret® (anakinra)
- Rituxan® (rituximab)
- Simponi® (golimumab)
- Cimzia® (certolizumab pegol)
- Actemra® (tocilizumab)

You may have a higher chance of getting a serious infection if you take ORENCIA with other biologic medicines for your RA or JIA.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new prescription.

How should I use ORENCIA?

- You may receive ORENCIA given by a healthcare provider through a vein in your arm (IV or intravenous infusion). It takes about 30 minutes to give you the full dose of medicine. You will then receive ORENCIA 2 weeks and 4 weeks after the first dose and then every 4 weeks.
- You may also receive ORENCIA as an injection under your skin (subcutaneous). If your healthcare provider decides that you or a caregiver can give your injections of ORENCIA at home, you or your caregiver should receive training on the right way to prepare and inject ORENCIA. Do not try to inject ORENCIA until you have been shown the right way to give the injections by your healthcare provider.
- Your healthcare provider will tell you how much ORENCIA to use and when to use it.
- **See the Instructions for Use at the end of this Patient Information leaflet for instructions about the right way to prepare and give your ORENCIA injections at home.**

What are the possible side effects of ORENCIA?

ORENCIA can cause serious side effects including:

- **infections.** ORENCIA can make you more likely to get infections or make the infection that you have get worse. Some patients have died from these

infections. Call your healthcare provider right away if you have any symptoms of an infection. Symptoms of an infection may include:

- fever
- feel very tired
- have a cough
- have flu-like symptoms
- warm, red, or painful skin

- **allergic reactions.** Allergic reactions can happen to people who use ORENCIA. Call your healthcare provider or go to the emergency room right away if you have any symptoms of an allergic reaction. Symptoms of an allergic reaction may include:
  - hives
  - swollen face, eyelids, lips, or tongue
  - trouble breathing
- **hepatitis B infection** in people who carry the virus in their blood. If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active while you use ORENCIA. Your healthcare provider may do a blood test before you start treatment with ORENCIA while you use ORENCIA.
- **vaccinations.** You should not receive ORENCIA with certain types of vaccines (live vaccines). ORENCIA may also cause some vaccinations to be less effective. Talk with your healthcare provider about your vaccination plans.
- **breathing problems in patients with Chronic Obstructive Pulmonary Disease (COPD).** Some people may get certain respiratory problems more often if you receive ORENCIA and have COPD. Symptoms of respiratory problems include:
  - COPD that becomes worse
  - cough
  - trouble breathing
- **cancer (malignancies).** Certain kinds of cancer have been reported in people using ORENCIA. It is not known if ORENCIA increases your chance of getting certain kinds of cancer.

Common side effects of ORENCIA include:

- headache
- upper respiratory tract infection
- sore throat
- nausea

In children and adolescents, other side effects may include:

- diarrhea
- cough

- fever
- abdominal pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ORENCIA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ORENCIA?

- Store ORENCIA in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Keep ORENCIA in the original package and out of the light.
- Do not freeze ORENCIA.
- Safely throw away medicine that is out of date or no longer needed.

Keep ORENCIA and all medicines out of the reach of children.

General information about the safe and effective use of ORENCIA

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information leaflet. Do not use ORENCIA for a condition for which it was not prescribed. Do not give ORENCIA to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about ORENCIA. If you would like more information, talk to your healthcare provider.

You can ask your pharmacist or healthcare provider for information about ORENCIA that is written for health professionals.

For more information, go to www.ORENCIA.com or call 1-800-ORENCIA.

What are the ingredients in ORENCIA?

Active ingredient: abatacept

Intravenous inactive ingredients: maltose, monobasic sodium phosphate, sodium chloride for administration

Subcutaneous inactive ingredients: sucrose, poloxamer 188, monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous, water for injection

This Patient Information has been approved by the U.S. Food and Drug Administration.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Revised October 2014

INSTRUCTIONS FOR USE
ORENCIA® (oh-REN-see-ah)
(abatacept)
Prefilled Syringe

Read and follow these Instructions for Use that come with your ORENCIA prefilled syringe before you start using it and each time you get a refill. Before you use ORENCIA prefilled syringe for the first time, make sure your healthcare provider shows you the right way to use it.

Do not remove the needle cover (the cap) until you are ready to inject ORENCIA. Do not put the needle cover back on the needle after you remove it.

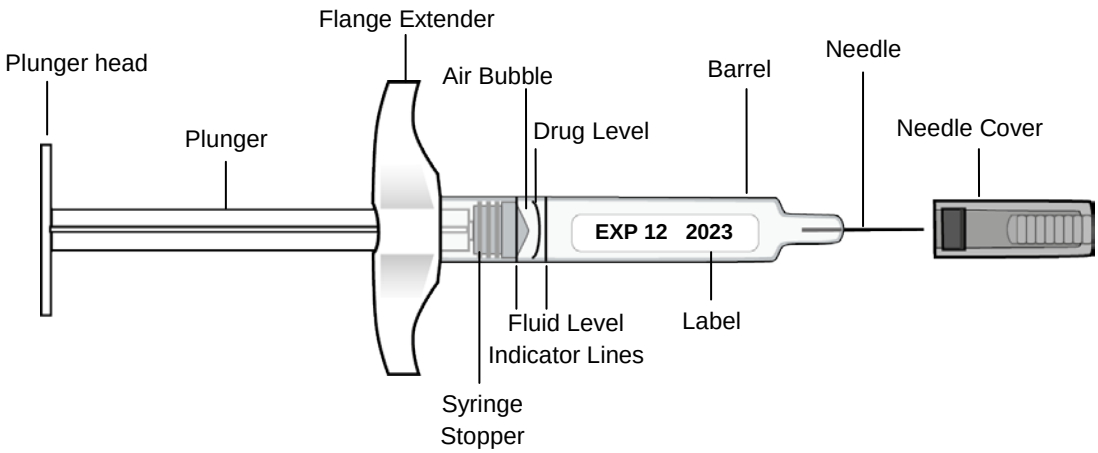


Figure A

- The ORENCIA prefilled syringe has a flange extender that makes it easier to hold the syringe and inject (**see Figure A**).

Supplies needed for your ORENCIA Prefilled Syringe Injection (see Figure B):

- a new ORENCIA prefilled syringe
- alcohol swab
- cotton ball or gauze
- adhesive bandage
- puncture resistant container (sharps container)

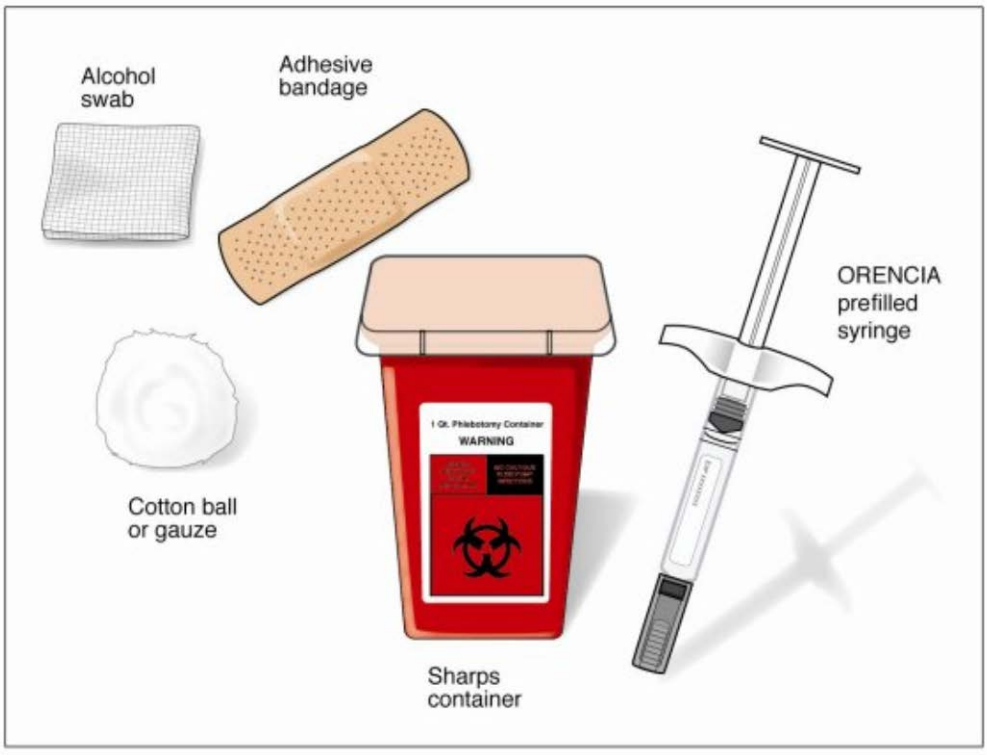


Figure B

STEP 1: Preparing for an ORENCIA Injection

Find a comfortable space with a clean, flat, working surface.

- Check the expiration date on the ORENCIA prefilled syringe (**see Figure A**). **Do not** use it if the expiration date has passed. Throw it away and get a new one.
- Remove 1 single-use ORENCIA prefilled syringe from the refrigerator and let it warm up for 30 to 60 minutes to allow it to reach room temperature.
    - **Do not** speed up the warming process in any way, such as using the microwave or placing the syringe in warm water.

Do not remove the needle cover while allowing ORENCIA prefilled syringe to reach room temperature.

- Keep your unused syringes in their original carton and keep in the refrigerator at 36°F to 46°F (2°C to 8°C). **Do not** freeze.
- Hold your ORENCIA prefilled syringe by the barrel with the covered needle pointing down (**see Figure C**).

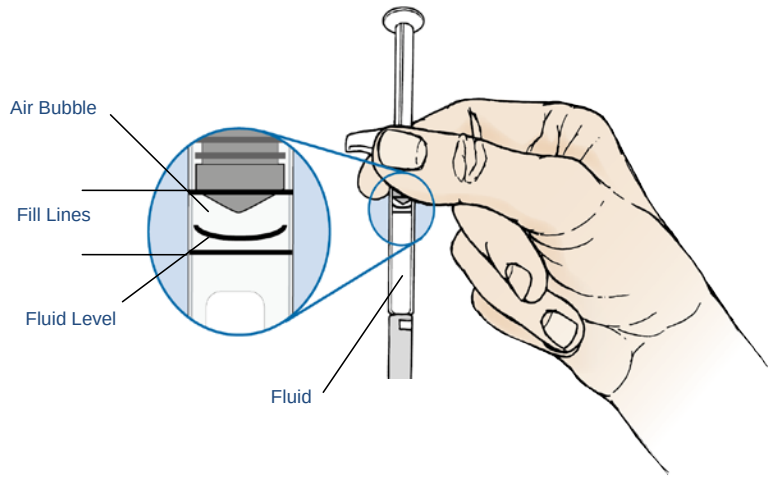


Figure C

- Check the liquid in the ORENCIA prefilled syringe. It should be clear and colorless to pale yellow. **Do not** inject ORENCIA if the liquid is cloudy, discolored, or has lumps or particles in it. Throw the syringe away and get a new one.
- Check that the amount of liquid in your ORENCIA prefilled syringe is the correct amount. The liquid should be between the two lines on the syringe barrel (**see Figure C**).
- **Do not** inject ORENCIA if it does not have the correct amount of liquid. Throw the ORENCIA prefilled syringe away and get a new one. It is normal to see an air bubble. There is no reason to remove it.
- Wash your hands well with soap and water.

STEP 2: Choose and Prepare an Injection Site

Choose an Injection Site

- The front of your thigh is a recommended injection area. You may use your abdomen except for the 2-inch area around your navel (**see Figure D**).
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. Do not attempt to use the upper arm area by yourself (**see Figure E**).

Rotate Injection Site

- Choose a different injection site for each new injection. You may use the same thigh for weekly injections, as long as each injection is at least 1 inch away from the last area you injected.
- Do not inject into areas where your skin is tender, bruised, red, scaly, or hard. Avoid any areas with scars or stretch marks.

Areas for self-injection and caregiver injection

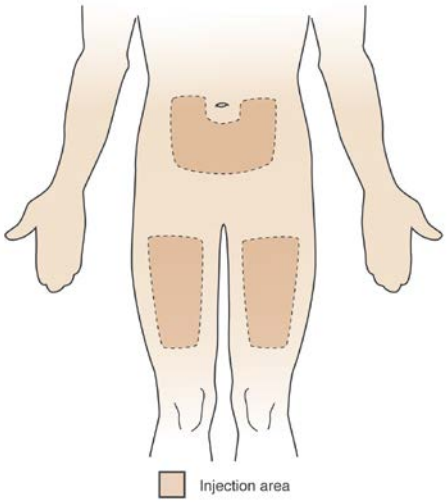


Figure D

Additional injection area for caregivers only

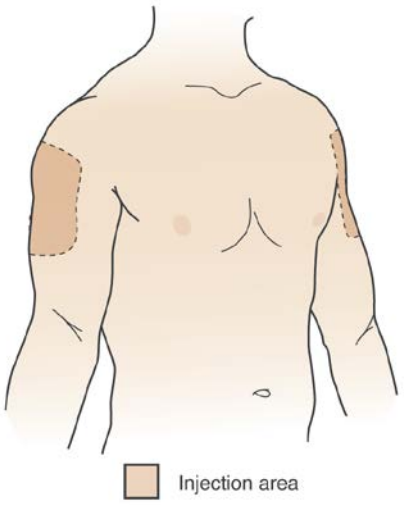


Figure E

Prepare the Injection Site

- Wipe the injection site with an alcohol swab in a circular motion and let it air dry. **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

STEP 3: Inject ORENCIA

- **Do not** remove the needle cover until you are ready to give the injection. Hold the barrel of the ORENCIA prefilled syringe with one hand and pull the needle cover straight off with your other hand (**see Figure F**). **Do not** touch the plunger while you remove the needle cover.

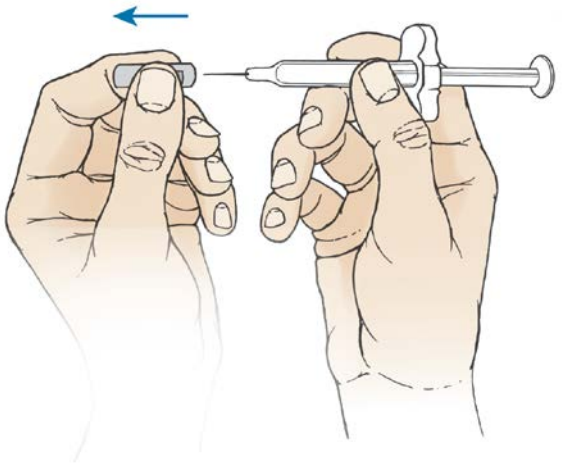


Figure F

- **Do not** put the needle cover back on the needle after you remove it. Throw away the needle cover in your household trash.
- **Do not** use the ORENCIA prefilled syringe if the needle looks damaged or bent.
- There may be a small air bubble in the ORENCIA prefilled syringe barrel. You do not need to remove it.
- You may notice a drop of fluid leaving the needle. This is normal and will not affect your dose.
- **Do not** touch the needle or let it touch any surfaces.
- **Do not** use the prefilled syringe if it is dropped without the needle cover in place.
- Hold the barrel of your ORENCIA prefilled syringe in one hand between the thumb and index finger (**see Figure G**).

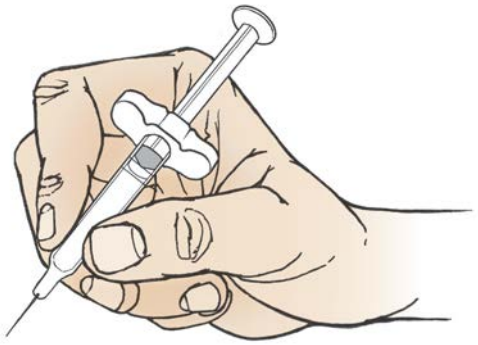


Figure G

- **Do not** pull back on the plunger of the syringe.
- Use your other hand and gently pinch the area of skin you cleaned. Hold firmly.
- Insert the needle with a quick motion into the pinched skin at a 45° angle (**see Figure H**).

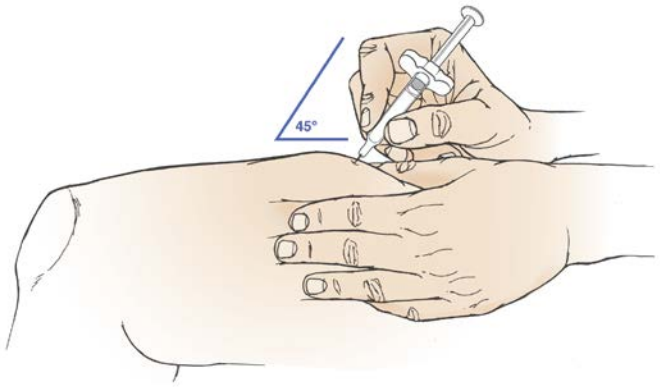


Figure H

- To inject all of the medicine, use your thumb to push down on the plunger head until the plunger head is pushed in as far as it will go (**see Figure I**).

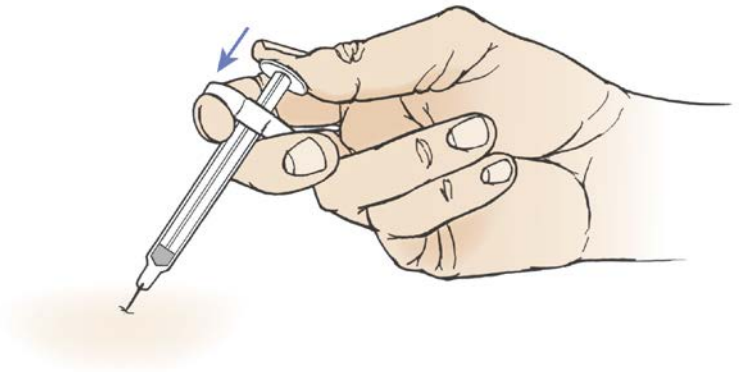


Figure I

- Remove the needle from the skin and let go of the surrounding skin.

After the Injection

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.

STEP 4: Disposal and Recordkeeping

- The ORENCIA prefilled syringe should not be reused.
- Put the used syringe into your puncture resistant container (see "**How do I throw away used syringes?**").
- **Do not** put the needle cover back on the needle.
- **If your injection is given by another person, this person must also be careful when removing the syringe and disposing of the syringe to prevent accidental needle stick injury and passing infection.**

How do I throw away used syringes?

Check with your healthcare provider or pharmacist for instructions about the right way to throw away used syringes. There may be special local or state laws about how to throw away used syringes.

- **Do not** throw away used syringes in the household trash and do not recycle them.
- Put used and empty ORENCIA prefilled syringes in a biohazard container made specifically for disposing of used syringes (called a “sharps” container) or in a hard plastic container with a screw-on cap (such as an empty detergent bottle) or in a metal container with a plastic lid (such as a coffee can). Sharps containers can be purchased at your local pharmacy or many retail outlets.
- When the container is full, tape around the cap or lid to make sure the cap or lid does not come off.
- **Keep ORENCIA prefilled syringes and the disposal container out of the reach of children.**

Record your Injection

- Write the date, time, and specific part of your body where you injected yourself. It may also be helpful to write any questions or concerns about the injection so you can ask your healthcare provider.

If you have questions or concerns about your ORENCIA prefilled syringe, please contact a healthcare provider familiar with ORENCIA or call our toll-free help line at 1-800-ORENCIA (1-800-673-6242).

Frequently Asked Questions

Injecting with the ORENCIA prefilled syringe

I feel a little bit of burning or pain during injection. Is this normal?

- When giving yourself an injection, you may feel a prick from the needle. Sometimes, the medicine can cause slight irritation near the injection site. This may happen and the discomfort should be mild to moderate. If you have any side effects, including pain, swelling, or discoloration near the injection site, contact your healthcare provider.

Traveling with ORENCIA prefilled syringes

How should I keep my prefilled syringes cool while traveling?

- If you need to take your prefilled syringes with you, store them in a cool carrier between 36°F to 46°F (2°C to 8°C) until you are ready to use.
- **Do not** freeze ORENCIA.

- Keep ORENCIA in the original carton and protected from light. Your healthcare provider may know about special carrying cases for injectable medicines.

Can I take my prefilled syringes on an airplane?

- Generally you are allowed to carry ORENCIA prefilled syringes with you on an airplane. **Be sure to carry the prefilled syringes with you on board the plane, and do not put them in your "checked" luggage.** You should carry ORENCIA prefilled syringes with you in your travel cooler at a temperature of 36°F to 46°F (2°C to 8°C) until you are ready to use.
- Keep ORENCIA in the original carton, with its original preprinted labels and protected from light.

What if my syringe does not stay cool for an extended period of time? Is it dangerous to use?

- Contact 1-800-ORENCIA (1-800-673-6242) for details.

If you have questions or concerns about your ORENCIA prefilled syringe, please contact a healthcare provider familiar with ORENCIA or call our toll-free help line at 1-800-ORENCIA (1-800-673-6242).

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised October 2014

INSTRUCTIONS FOR USE
ORENCIA® (oh-REN-see-ah)
(abatacept)
Prefilled Syringe with UltraSafe Passive® Needle Guard

Read and follow these Instructions for Use that come with your ORENCIA prefilled syringe before you start using it and each time you get a refill. Before you use ORENCIA prefilled syringe for the first time, make sure your healthcare provider shows you the right way to use it.

Do not remove the needle cover (the cap) until you are ready to inject ORENCIA. Do not put the needle cover back on the needle after you remove it.

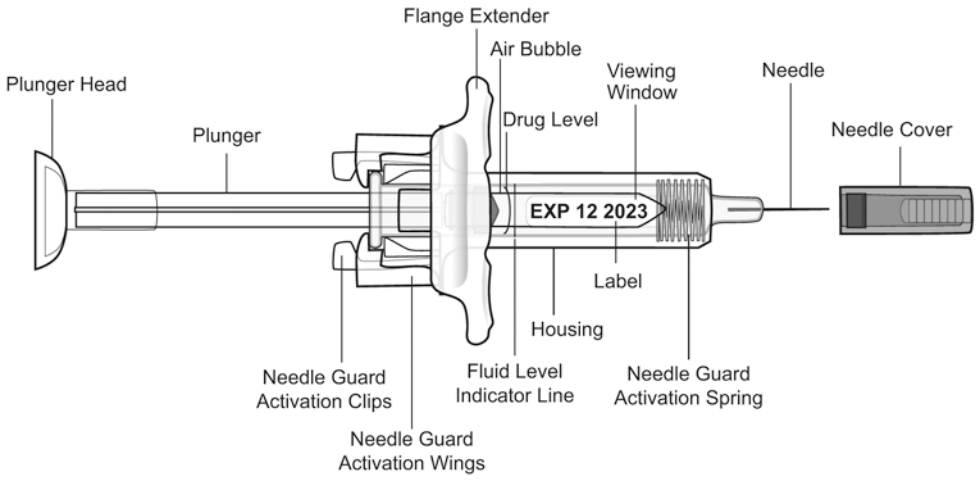


Figure A

- The ORENCIA prefilled syringe has a flange extender that makes it easier to hold the syringe and inject, and a needle guard that automatically extends over the needle after the injection is complete (**see Figure A**).

Supplies needed for your ORENCIA Prefilled Syringe Injection (see Figure B):

- a new ORENCIA prefilled syringe
- alcohol swab
- cotton ball or gauze
- adhesive bandage
- puncture resistant container (sharps container)

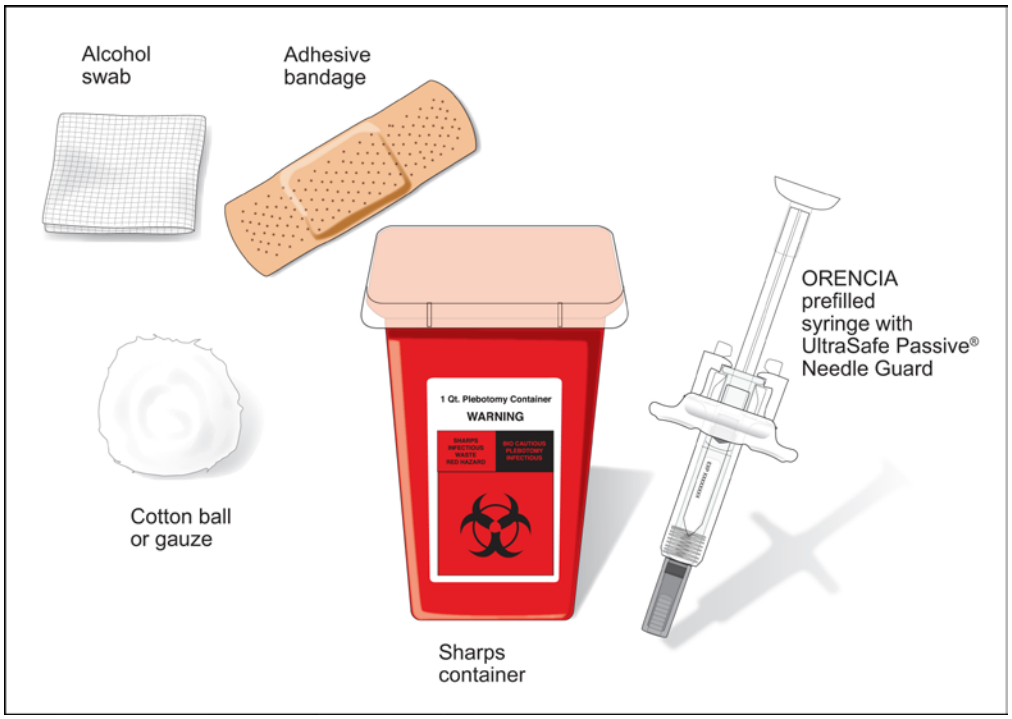


Figure B

STEP 1: Preparing for an ORENCIA Injection

Find a comfortable space with a clean, flat, working surface.

- Check the expiration date on the ORENCIA prefilled syringe (**see Figure A**). **Do not** use it if the expiration date has passed. Throw it away and get a new one.
- Remove 1 single-use ORENCIA prefilled syringe from the refrigerator and let it warm up for 30 to 60 minutes to allow it to reach room temperature.
    - **Do not** speed up the warming process in any way, such as using the microwave or placing the syringe in warm water.

Do not remove the needle cover while allowing ORENCIA prefilled syringe to reach room temperature.

- Keep your unused syringes in their original carton and keep in the refrigerator at 36°F to 46°F (2°C to 8°C). **Do not** freeze.
- Hold your ORENCIA prefilled syringe by the housing with the covered needle pointing down (**see Figure C**).

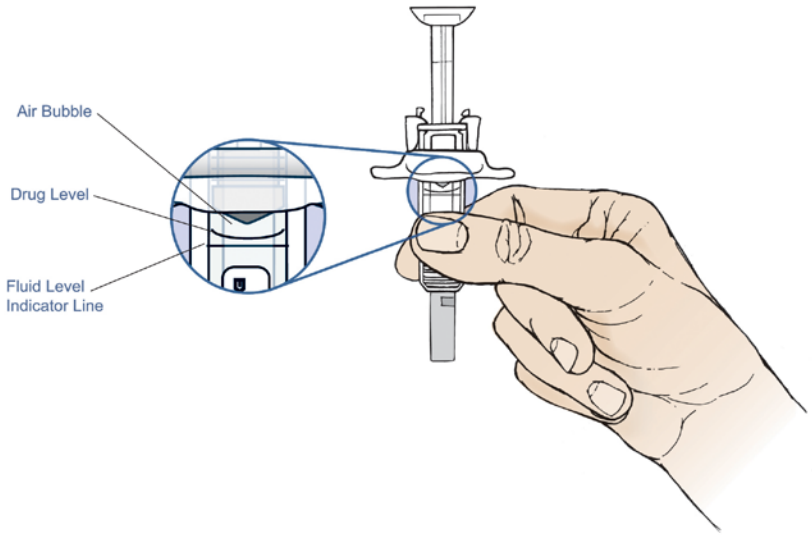


Figure C

- Check the liquid in the ORENCIA prefilled syringe. It should be clear and colorless to pale yellow. **Do not** inject ORENCIA if the liquid is cloudy, discolored, or has lumps or particles in it. Throw the syringe away and get a new one.
- Check that the amount of liquid in your ORENCIA prefilled syringe is the correct amount. Confirm the drug level is above the fluid level indicator line (**see Figure C**).
- **Do not** inject ORENCIA if it does not have the correct amount of liquid. Throw the ORENCIA prefilled syringe away and get a new one. It is normal to see an air bubble. There is no reason to remove it.
- Wash your hands well with soap and water.

STEP 2: Choose and Prepare an Injection Site

Choose an Injection Site

- The front of your thigh is a recommended injection area. You may use your abdomen except for the 2-inch area around your navel (**see Figure D**).
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. Do not attempt to use the upper arm area by yourself (**see Figure E**).

Rotate Injection Site

- Choose a different injection site for each new injection. You may use the same thigh for weekly injections, as long as each injection is at least 1 inch away from the last area you injected.
- Do not inject into areas where your skin is tender, bruised, red, scaly, or hard. Avoid any areas with scars or stretch marks.

Areas for self-injection and caregiver injection

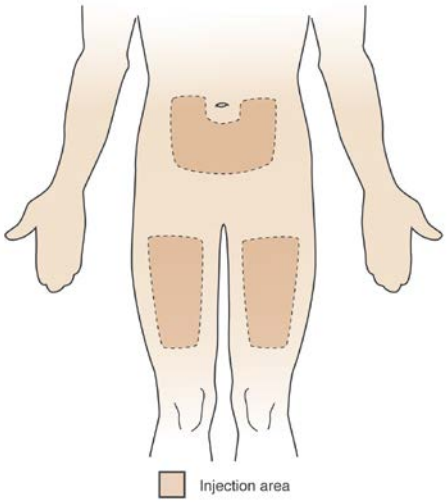


Figure D

Additional injection area for caregivers only

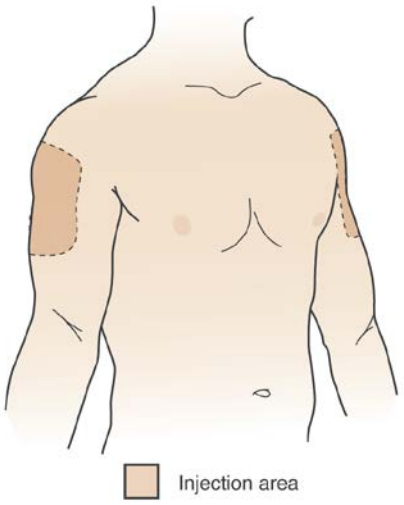


Figure E

Prepare the Injection Site

- Wipe the injection site with an alcohol swab in a circular motion and let it air dry. **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

STEP 3: Inject ORENCIA

- **Do not** remove the needle cover until you are ready to give the injection. Hold the housing of the ORENCIA prefilled syringe with one hand and pull the needle cover straight off with your other hand (**see Figure F**). **Do not** touch the plunger while you remove the needle cover.

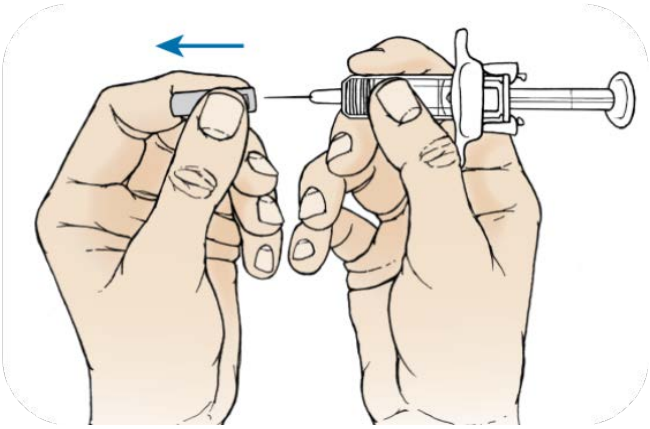


Figure F

- **Do not** put the needle cover back on the needle after you remove it. Throw away the needle cover in your household trash.

- **Do not** use the ORENCIA prefilled syringe if the needle looks damaged or bent.
- There may be a small air bubble in the ORENCIA prefilled syringe housing. You do not need to remove it.
- You may notice a drop of fluid leaving the needle. This is normal and will not affect your dose.
- **Do not** touch the needle or let it touch any surfaces.
- **Do not** use the prefilled syringe if it is dropped without the needle cover in place.
- Hold the housing of your ORENCIA prefilled syringe in one hand between the thumb and index finger (**see Figure G**).

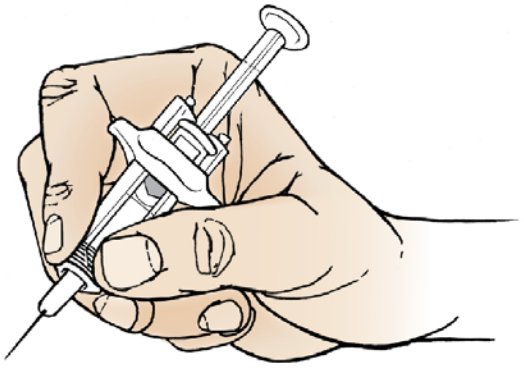


Figure G

- **Do not** pull back on the plunger of the syringe.
- Use your other hand and gently pinch the area of skin you cleaned. Hold firmly.
- Insert the needle with a quick motion into the pinched skin at a 45° angle (**see Figure H**).

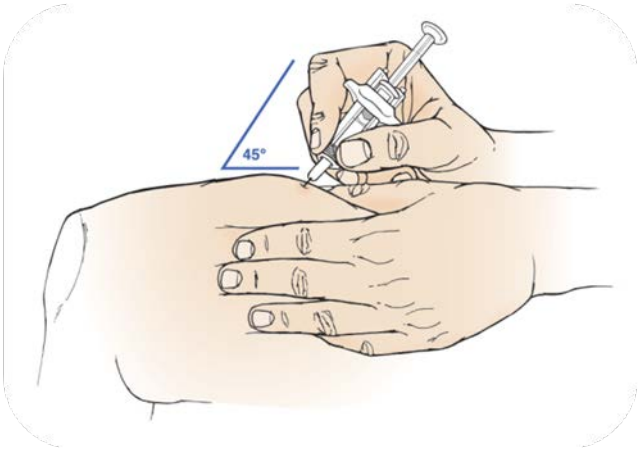


Figure H

- To inject all of the medicine, use your thumb to push the plunger until the plunger head is pushed in as far as it will go.

- Slowly lift your thumb from the plunger head. This allows the needle to be completely covered by the needle guard as it is removed from the skin (**see Figure I**).

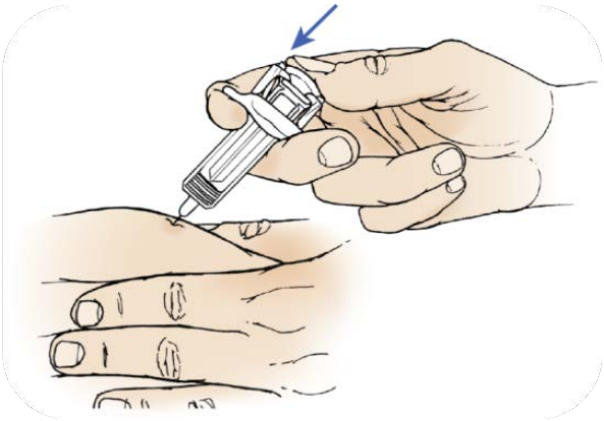


Figure I

- Remove the prefilled syringe and let go of the surrounding skin (**see Figure J**).

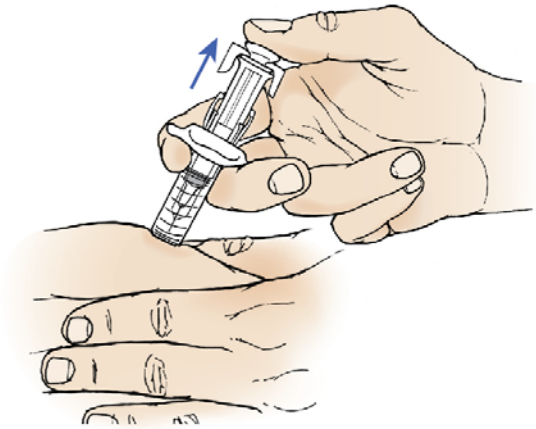


Figure J

After the Injection

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.

STEP 4: Disposal and Recordkeeping

- The ORENCIA prefilled syringe should not be reused.
- Put the used syringe into your puncture resistant container (see "**How do I throw away used syringes?**").
- **Do not** put the needle cover back on the needle.

- **If your injection is given by another person, this person must also be careful when removing the syringe and disposing of the syringe to prevent accidental needle stick injury and passing infection.**

How do I throw away used syringes?

Check with your healthcare provider or pharmacist for instructions about the right way to throw away used syringes. There may be special local or state laws about how to throw away used syringes.

- **Do not** throw away used syringes in the household trash and do not recycle them.
- Put used and empty ORENCIA prefilled syringes in a biohazard container made specifically for disposing of used syringes (called a “sharps” container) or in a hard plastic container with a screw-on cap (such as an empty detergent bottle) or in a metal container with a plastic lid (such as a coffee can). Sharps containers can be purchased at your local pharmacy or many retail outlets.
- When the container is full, tape around the cap or lid to make sure the cap or lid does not come off.
- **Keep ORENCIA prefilled syringes and the disposal container out of the reach of children.**

Record your Injection

- Write the date, time, and specific part of your body where you injected yourself. It may also be helpful to write any questions or concerns about the injection so you can ask your healthcare provider.

If you have questions or concerns about your ORENCIA prefilled syringe, please contact a healthcare provider familiar with ORENCIA or call our toll-free help line at 1-800-ORENCIA (1-800-673-6242).

Frequently Asked Questions

<u>Injecting with the ORENCIA prefilled syringe</u>

I feel a little bit of burning or pain during injection. Is this normal?

- When giving yourself an injection, you may feel a prick from the needle. Sometimes, the medicine can cause slight irritation near the injection site. This may happen and the discomfort should be mild to moderate. If you have any side effects, including pain, swelling, or discoloration near the injection site, contact your healthcare provider.

Traveling with ORENCIA prefilled syringes

How should I keep my prefilled syringes cool while traveling?

- If you need to take your prefilled syringes with you, store them in a cool carrier between 36°F to 46°F (2°C to 8°C) until you are ready to use.
- **Do not** freeze ORENCIA.
- Keep ORENCIA in the original carton and protected from light. Your healthcare provider may know about special carrying cases for injectable medicines.

Can I take my prefilled syringes on an airplane?

- Generally you are allowed to carry ORENCIA prefilled syringes with you on an airplane. **Be sure to carry the prefilled syringes with you on board the plane, and do not put them in your "checked" luggage.** You should carry ORENCIA prefilled syringes with you in your travel cooler at a temperature of 36°F to 46°F (2°C to 8°C) until you are ready to use.
- Keep ORENCIA in the original carton, with its original preprinted labels and protected from light.

What if my syringe does not stay cool for an extended period of time? Is it dangerous to use?

- Contact 1-800-ORENCIA (1-800-673-6242) for details.

If you have questions or concerns about your ORENCIA prefilled syringe, please contact a healthcare provider familiar with ORENCIA or call our toll-free help line at 1-800-ORENCIA (1-800-673-6242).

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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